PETITION
PP97-1

Received
1/30/98

CPSA 6 (b)(1) Cleared
8/11/97
No Mfrs/PrvtLblrs or
Products Identified
Excepted by 6(a) INAD
Firms Notified, EXCUSED
Comments Processed.

Petition

ORPHAN MEDICAL
13911 Ridgedale Drive, Suite 475
Minnetonka, Minnesota 55305
612-513-6900

NDA #20-772
July 10, 1997

Request for a Stay of Enforcement for the Prescription Drug Sucraid™(sacrosidase) oral solution

Petition for Exemption from the Poison Prevention Packaging Act Requirements for the Prescription Drug Sucraid™(sacrosidase) oral solution

PP97-1

PP 97-1

ORPHAN MEDICAL

July 10, 1997

Office of the Secretary
Consumer Product Safety Commission
Washington, DC 20207-0001

SUBJECT: Request for a Stay of Enforcement for the Prescription Drug Sucraid™ (sacrosidase) oral solution

Dear Sir/Madam:

Orphan Medical, Inc. respectfully requests a stay of enforcement, until the exemption, from special packaging requirements, can be reviewed and granted from the Consumer Products Safety Commission for the prescription drug Sucraid (sacrosidase) oral solution. This exemption is being submitted under 16 CFR 1702 for the above referenced prescription drug product from the special packaging requirements under 1700.14(a), specifically, 16 CFR 1700.14(a) (10).

A New Drug Application (NDA #20-772) for Sucraid (sacrosidase) oral solution was submitted under section 505(b) of the Food, Drug and Cosmetic Act (FD&C Act) on May 6, 1997. This medication has been designated an Orphan Drug under section 316.20 (number 93-786, designation date December 10, 1993). Sucraid (sacrosidase) oral solution is used for the treatment of congenital sucrase-isomaltase deficient patients (CSID) who are missing the endogenous digestive enzyme. Currently, there are no alternative drug treatments available for the approximately 3,000 - 10,000 cases of CSID patients in the United States. Priority. review status has been granted within the Food and Drug Administration. Priority review classification under the Prescription Drug User Fee Act of 1992 (PDUFA) determines the review time frame the application receives, which in this case is six months from the date of receipt (May 7, 1997).

Based on priority review status, the lack of toxicity associated with sacrosidase oral solution, limited distribution of the product, and the medical necessity associated with the drug,

13911 Ridgedale Drive, Suite 475 • Minnetonka, Minnesota 55305 • 612-513-6900 • Fax: 612-541-9209

Orphan Medical, Inc., respectfully requests the Consumer Product Safety Commission grant a stay of enforcement for Sucraid (sacrosidase) oral solution until this exemption review process from special packaging requirements has been completed and can be granted.

All correspondence regarding this request for a stay of enforcement and for exemption to the Poison Prevention Packaging Act Requirements should be directed to:

Dayton T. Reardan, Ph.D., RAC
Vice President of Regulatory Affairs
Orphan Medical, Inc.
13911 Ridgedale Drive, Suite 475
Minnetonka, MN 55305

Sincerely,

Dayton T. Reardan, Ph.D., RAC
Vice President of Regulatory Affairs

CC: Melodi McNeil (NDA 20-772)
Laura Washburn

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PP 97-1

ORPHAN MEDICAL

July 10, 1997

Office of the Secretary
Consumer Product Safety Commission
Washington, DC 20207-0001

SUBJECT: . Petition for Exemption from the Poison Prevention Packaging Act Requirements for the Prescription Drug Sucraid™ (sacrosidase) oral solution

Dear Sir/Madam:

This petition for exemption from the Poison Prevention Packaging Act is being submitted under 16 CFR 1702. It requests exemption for the above referenced drug product from the special packaging requirements under 1700.14(a), specifically, 16 CFR 1700.14(a)(10). As requested by 16 CFR 1702.2, five (5) copies of this petition are enclosed herewith in addition to the original. Three (3) Sucraid investigational drug packages have been provided as requested.

A New Drug Application (NDA #20-772) for Sucraid (sacrosidase) oral solution was submitted under section 505(b) of the Food, Drug and Cosmetic Act (FD&C Act) on May 6, 1997. This medication has been designated an Orphan Drug under section 316.20 (number 93-786, designation date December 10, 1993). Sucraid is used for the treatment of congenital sucrase-isomaltase deficient patients (CSID) who are missing the endogenous digestive enzyme. The active moiety in Sucraid is sacrosidase, a yeast-derived form of the sucrase enzyme. Currently, there are no alternative drug treatments available for CSID patients numbering approximately 3,000 - 10,000 cases in the United States. Priority review status has been granted within the Food and Drug Administration. Priority review classification under the Prescription Drug User Fee Act of 1992 (PDUFA) determines the review time frame the application receives, which in this case is six months from the date of receipt (May 7, 1997). Based on priority review status, the lack of toxicity associated with sacrosidase oral solution, limited distribution of the product, and the medical necessity associated with the drug, Orphan Medical, Inc. has requested the Consumer Product Safety Commission to grant a stay of enforcement

for Sucraid until the process has been completed and this exemption from special packaging requirements can be reviewed and granted.

Under 16 CFR 1015.18, information that Orphan Medical, Inc. deems proprietary and trade secret is requested for exemption from disclosure under 5 USC 552(b) (4) is in bold print as follows:

The drug product is packaged in [redacted] plastic bottles which are blow-molded, filled, and sealed. Uponsealing, the bottle becomes a self-contained container/closure system. (A cap is included to assist in the opening of the bottle at the time of administration and for resealing the bottle for future use.)

The [redacted] cap is made of [redacted] The cap is placed on the sealed bottle after filling. The cap has a small spike on the inside which can be used to pierce the sealed bottle tip at the time of first use. It cannot come in contact with the drug product until the bottle is opened. Labeling requires the product to be discarded four weeks after opening.

The scoop is made of white [redacted] which is composed of [redacted] resins. It is suitable for food contact use (21 CFR 177.1640). The scoop has no product contact except for measuring the dose. The scoop is placed between the two bottles in the carton.

We respectfully request the confidential information (highlighted in bold) not be maintained in the public file. Orphan Medical, Inc., however, intends in good faith to assist the Commission in the defense of any judicial proceeding that might thereafter be brought to compel the disclosure of information which the Commission has determined to be a trade secret or privileged or confidential commercial information.

JUSTIFICATION FOR THE: EXEMPTION

The justification for the exemption, required under 16 CFR 1702.3, is based on the following grounds:

I) the lack of need for special packaging to protect young children from serious injury or illness from the substance based on the lack of toxicity and lack of adverse human experience

and

2) special packaging is not technologically feasible, practicable, or appropriate for the substance.

1) JUSTIFICATION BASED UPON LACK OF NEED BASED ON LACK OF TOXICITY AND LACK OF ADVERSE HUMAN EXPERIENCE

Lack of Toxicity

Prior to the filing of NDA #20-772, Orphan Medical and FDA agreed that no nonclinical toxicity studies were required. This conclusion regarding sacrosidase's inherent lack of toxicity was based upon the following:

(1) Yeast-derived sacrosidase has been widely utilized within the human food industry for decades in the confectionery and baking industry. It is a Generally Recognized as Safe (GRAS) food material under FDA provision 21 CFR § 170.30 due to its long history of safe use in human food. The sponsor is unaware of any reported toxicity associated with the use of sacrosidase as a food product.

(2) Because sacrosidase is a large macromolecule, it will not be transported intact across the gastrointestinal mucosa and into the systemic circulation following oral ingestion. Thus, no systemic toxicity directly from the sacrosidase molecule is feasible.

(3) Because sacrosidase is a naturally occurring enzyme with a glycoprotein structure, it will be digested to peptides and eventually amino acids within the small intestine. These metabolic products will be absorbed into the circulation and utilized as nutrients.

(4) Several years of clinical experience with the yeast-derived oral sacrosidase solution in patients as young as 5 months of age have not revealed any evidence of significant toxicity or intolerance.

Orphan Medical has reviewed the scientific literature via computerized database searches and has determined that no studies have been published that examine the toxicity of the enzyme sucrase either endogenous human sucrase or exogenous yeast-derived sucrase.

Human Experience Data

In the development of most new drugs the new chemical entity is initially evaluated in biological screens (e.g. biochemistry, pharmacology, virology, microbiology) where an activity of interest is detected and measured. Over a period of time, and using several or many animal models, the scientists attempt to identify the specific compound with the greatest activity indicative of efficacy and the least toxicity. Usually a battery of in vitro and in vivo models are used in this endeavor and

thousands of compounds tested before a single compound is chosen for development. After a further one or more years of preclinical development the compound is eventually studied in humans.

Sucraid™ (sacrosidase) oral solution had a very different development path. Congenital sucrase-isomaltase deficiency disease (CSID) had been known for years before the logic of replacing the missing endogenous digestive enzyme sucrase-isomaltase was clinically attempted. The availability of the yeast-derived enzyme as a food grade product meant that animal testing was not required to assess its toxicity profile. Enzyme replacement in diseases such as Gaucher's Disease originally involved a difficult extraction of the enzyme from human tissue (placenta), but the enzyme sacrosidase was readily available from yeast manufacturers, and in fact is widely used by commercial bakeries, confection and candy makers.

The human evaluation of therapeutic efficacy was straightforward and the resulting efficacy data extremely clear cut and convincing. If an animal model of CSID existed, it would have been of interest to study Sucraid in this model, but no model does in fact exist.

Given the existence of substantial human data, there is no scientific need to retrospectively evaluate and measure the enzyme for its nonclinical efficacy. Other pharmacological tests were not deemed necessary because of safety data obtained in humans, the food status of the enzyme, and the large benefit to risk ratio of the enzyme in patients with the rare disease congenital sucrase-isomaltase deficiency (CSID).

Sucraid consists of approximately 1.5 mg/mL of protein in an aqueous solution containing 50% glycerol and 50% water at an unbuffered slightly acidic pH of 4.6. This product is derived from baker's yeast *(saccharomyces cerevisiae)* and is the same formulation used extensively in the food and candy industry. The amounts utilized in such products as soft center chocolate coated cherries is a fraction (<5%) of the therapeutic amounts utilized to obtain the pharmacologic effect in patients with congenital sucrase-isomaltase deficiency. The protein contains a known amino acid sequence which is heavily glycosylated. The product contains no neurotropic or narcotic like compounds. It is metabolized to constituent amino acids and sugars in the digestive tract. There is no known or theoretical potential for abuse of this drug. The drug produces no "high" and while it has a mild sweet taste, it would certainly not be considered to produce a gastric high such as other sweet or chocolate based foods. Therefore, the likelihood of drug abuse is for all practical purposes is zero percent (0%).

Overdosage of the product has been considered by Orphan Medical. The most toxic component is the glycerol which makes up 50% of the product by weight and is an osmotic diuretic. The product provided in 4 ounce (118 mL) containers with a very small opening through which to obtain product. Should a child ingest the full contents of one bottle of Sucraid, they would receive the equivalent of 150 mg of: protein, 59 mL of water, and 59 mL of glycerol. The 150 mg of protein and the 59 mL of water are negligible given even recommended daily requirements for infants. A full dose of 59 mL of glycerol into a two year old child weighing 10 kg would be the equivalent of (59 mL)X(1.2 g/mL) = 7.1 g/kg. The toxicity and safety of is deemed Generally Recognized as Safe (GRAS) by the Food and Drug Administration as a multiple purpose food substance in food for human consumption (21 CFR 182.1320). Glycerol is currently approved for use in multiple therapeutic products (Physicians Desk Reference 1996). The daily dose of the approved drug, OSMOGLYN, is 5 times that of the daily dose of Sucraid, per kg of body weight.

Therefore, if a child of 10 kg were to ingest the entire 4 oz. bottle of Sucraid, it is our assessment that there would be no significant toxic effect, particularly if the patient is kept hydrated. The proposed product labeling indicates the osmotic diuretic nature of the glycerol and the need for hydration should someone ingest an overdose of this product.

No cases of accidental or purposeful overdose have been reported but the protein chemical nature of the sacrosidase enzyme material and the fact that it is broken down in the intestinal tract following ingestion to nutrient peptides and amino acids supports the general principle that there is no significant toxicological effect.

Relevant Experimental Data

Three clinical trials have been conducted using Sucraid (sacrosidase) oral solution. None of the adverse events recorded at any time for patients during these three clinical trials were rated as probably or definitely drug-related by the clinical investigators. Although a number of adverse events were reported among these three trials, the vast majority fell into two categories: (1) they were symptoms of a concurrent illness common to the pediatric population such as flu, upper respiratory infections, or otitis media, or (2) they were GI symptoms commonplace to congenital sucrase-isomaltase deficiency (CSID) such as diarrhea, nausea, vomiting, or abdominal pain.

Human Experimental Data Involving the Testing of Human **Subjects**

study S-l

The objective of this trial was to evaluate the effect of sacrosidase on breath hydrogen excretion and gastrointestinal symptoms following the ingestion of a large sucrose load, and to establish a dose range of sacrosidase which allows the consumption of a normal sucrose containing diet.

patients were evaluated to confirm CSID diagnosis and trial eligibility prior to commencement of the breath hydrogen phase. During the breath hydrogen phase, patients were to undergo two randomized breath hydrogen tests, which entailed ingesting sucrose followed by placebo or sacrosidase. During each test, and for a period of eight hours thereafter, gastrointestinal symptoms were to be recorded on a symptom diary. The breath hydrogen tests were to be separated by one week. During the dose-response phase, patients were instructed to maintain a normal sucrose diet while receiving each of four concentrations of sacrosidase (1:100 dilution, 1:1,000 dilution, 1:10,000 dilution, and 1:100,000 dilution) in random order, for a period of 14 days each. Stool frequency and consistency measures, as well as gastrointestinal symptoms, were to be recorded on a daily basis. Adverse events were collected throughout the trial.

Patients were dosed using a 14-day randomized crossover on each of 4 doses (dilutions) of liquid sacrosidase:

Treatment 1: 1:100 dilution
Treatment 2: 1:1,000 dilution
Treatment 3: 1:10,000 dilution
Treatment 4: 1:100,000 dilution

The dose used was 1 mL/meal or snack orally administered, added to 1 ounce of liquid (water, milk, juice, infant formula).

The breath hydrogen phase consisted of one week (two single doses given one week apart); the dose-response phase consisted of eight weeks (14 days on each of the four sacrosidase doses).

In the first trial (S-l) 8 of the 14 patients in the safety population experienced at least one adverse event. (See Table 8.8.4 below for details of adverse events). Symptoms associated with these events included fever, flu, headache, vomiting, congestion, side pain, runny stools, rectal bleeding, and ear problems. There were a total of 17 adverse events reported, eight of which were considered by the Clinical Investigator to be related to a concurrent illness while nine were rated as unknown or were not indicated to be drug related.

No adverse events were rated by the Clinical Investigator as possibly or probably drug related. There were no serious adverse events or withdrawals due to adverse events during this trial.

TABLE 8.8.4
TRIAL S-l (OMC-SUC-1): SAFETY POPULATION
LISTING OF PATIENTS WITH ADVERSE EVENTS

Pt Number/ Initials	Adverse Event (Original Term)	Adverse Event (COSTART term)	Study Phase/ Tx & Dose	Resolution of Adverse Event	Relationship to Study Drug
l/SW	Nausea/vomited	Nausea Vomit	BHT Placebo	NI	NI
	Lots of gagging	Vomit	BHT Enzyme	NI	NI
2/CB	Cold	Rhinitis	D/R 1:1,000	Cold medicine "Triaminic" given 1/2 tsp. x 3 days	NI
	Cranky, irritable	Nervousness	D/R 1:100	NI	NI
	Slight bleeding from rectum	Hem Rectal	D/R 1:100,000	NI	NI
4/BG	"caught viral and bad runny stools"	React Uneval Diarrhea	D/R 1:100	NI	Concurrent illness - not related'
8/DM	"achiness, sick, nausea"	Flu Synd	BHT Placebo	NI	NI
	Nausea	Nausea	BHT Enzyme	NI	NI
	"some bleeding from rectum with movement"	Hem Rectal	D/R 1:1000	"went away on its own-"	NI

BHT = Breath Hydrogen Test Phase, D/R = Dose-Response Phase, NI = Not indicated

TABLE 8.8.4
TRIAL S-l (OMC-SUC-1) : SAFETY POPULATION
LISTING OF PATIENTS WITH ADVERSE EVENTS

Pt Number/ Initials	Adverse Event (Original Term)	Adverse Event (COSTART term)	Study Phase/ Tx & Dose	Resolution of Adverse Event	Relationship to Study Drug
8/DM	"side pain"	Pain Flank	D/R 1:10,000	"took muscle relaxants for cramps "	Concurrent illness - not related
9/CS	"fever, vomiting for a few days"	Fever Vomit	D/R 1:10,000	NI	Concurrent illness - not related
	"ear problems, congestion, left ear infection"	Ear Dis Rhinitis Infect	D/R 1:1,000	"gave her moxil"	Concurrent illness - not related
11/CK	Felt faint 2 hours after sucrose dose	Dizziness	BHT Placebo	NI	NI
13/JP	"had a stomach flu for a couple of days"	Flu Synd	D/R 1:10,000	NI	Concurrent illness - not related
	"did not feel as well, ,did not eat as much, color and hair not as good as first bottle"	React Uneval Anorexia React Uneval	D/R 1:1,000	NI	NI
15/BE	Mild headache	Headache	BHT Placebo	NI	NI
	"flu Wed-Fri (Day 1,2,3), too much Halloween candy"	Flu Synd React Uneval	D/R 1:100,000	NI	Concurrent illness - not related

BHT = Breath Hydrogen Test Phase, D/R = Dose-Response Phase, NI = Not indicated

Trial S-2

The objective of this trial was to test the efficacy of yeast-derived liquid sacrosidase in treating patients of all ages with congenital sucrase-isomaltase deficiency (CSID). The specific hypotheses to be tested were: 1) sacrosidase will prevent or blunt the expected rise in breath hydrogen excretion when a patient with CSID ingests a large sucrose load, and 2) sacrosidase will prevent gastrointestinal symptoms when a patient with CSID ingests a diet containing normal amounts of sucrose.

Patients were evaluated for trial eligibility prior to commencement of the breath hydrogen phase. During the breath hydrogen phase, patients were to undergo three breath hydrogen tests (BHTs), which entailed. ingesting sucrose (2g/kg) followed by placebo, sacrosidase, or milk/sacrosidase. During each 3-hour breath test, and for up to 24 hours thereafter, gastrointestinal symptoms were to be recorded on a symptom diary. Each breath test was to be separated by one week during which the patient was to maintain a sucrose-free/low starch diet. During the dose-response phase, patients were instructed to maintain a normal sucrose-containing diet while receiving each of four concentrations of sacrosidase (full-strength, 1:10 dilution, 1:100 dilution, 1:1,000 dilution) in random order, for a period of 10 days each. Stool frequency and consistency measures, as well as gastrointestinal symptoms and dietary data, were recorded on a daily basis. Adverse events were collected throughout the trial.

The dosing of the patients was a 14-day randomized crossover on each of 4 doses (dilutions) of liquid sacrosidase:

Treatment 1.: Full-strength enzyme
Treatment 2: 1:10 dilution
Treatment 3: 1:100 dilution
Treatment 4: 1:1,000 dilution

The dose taken each time was:

- 1 mL/meal for patients weighing no more than 15 kg
- 2 mL/meal for patients weighing more than 15 kg

The drug was administered orally approximately five minutes after beginning each meal, added to 2-4 ounces of water.

A listing of patients in the safety population who experienced adverse events during the OMC-SUC-:2 (S-2) trial is presented in Table 8.8.5. All of the events are listed both using the Clinical Investigator's *(or* parent's) original description as well as the COSTART standardized term. The trial phase and dose at the onset of the'adverse event and

the resolution of the event (if known) are included in this table. For the purpose of this report, an adverse event was considered to consist of the Clinical Investigator's complete description of an event on a given date, even though such descriptions may have included more than one symptom or observation.

Overall, 26 of the 34 patients in the Trial S-2 safety population experienced at least one adverse event. Most of the adverse events (49/95, 52%) were attributed to concurrent illnesses and were not considered by the Clinical Investigator to be related to sacrosidase. Twelve patients experienced adverse events which were all attributed to concurrent illnesses and were not considered by the Clinical Investigator to be related to sacrosidase. Symptoms associated with these events included abdominal pain, viral infection, strep throat, ear infection, sore throat, fever, malaise, rash, diarrhea, cramping, cough, and runny nose.

Eleven of the 26 patients experienced one or more adverse events that were considered by the Clinical Investigator to be possibly related to sacrosidase. Symptoms associated with these events included abdominal pain, nausea, vomiting, constipation, diarrhea, dehydration, cramps, frequent bowel movements, headache, insomnia, irritability, shock and wheezing. It should be noted, however, that many of these events may have been symptoms of sucrose malabsorption that are typical of patients with CSID and were therefore not unusual for this patient population. Furthermore, most of the patients in the safety population completed both the breath hydrogen phase and the dose-response phase of the trial, suggesting that sacrosidase was well-tolerated by most patients.

TABLE 8.8.5

TRIAL S-2 (OMC-SUC-2): SAFETY POPULATION
LISTING OF PATIENTS WITH ADVERSE EVENTS

Pt Number/ Initials	Adverse Event (Original Term)	Adverse Event (COSTART Term)	Study Phase/ Tx & Dose	Resolution of Adverse Event	Relationship to Study Drug
02/TG	Vomited	Vomit	During BHT / NI	NI	NI
03/RM	Throwing-up during & after BHT	Vomit	During BHT / Enzyme	NI	Possibly related
	Vomited	Vomit	After BHT / Enzyme	NI	Concurrent illness - not related
	Vomited, not feeling good	Vomit	After BHT / Enzyme	NI	Concurrent illness - not related
06/JR	Started wheezing	Asthma	During BHT / Milk & Enzyme	To ER - ADM. to ICU - dropped from study	Possibly related
08/CB	Has GI bug	Flu Synd	NI / NI	D/R phase delayed	Concurrent illness - not related
11/LA	Nausea	Nausea	NI / NI	NI	NI

BHT = Breath Hydrogen Test Phase
D/R = Dose-Response Phase
NI = Not indicated
NA = Not applicable

TABLE 8.8.5
TRIAL S-2 (OMC-SUC-2): SAFETY POPULATION
LISTING OF PATIENTS WITH ADVERSE EVENTS

Pt Number/ Initials	Adverse Event (Original Term)	Adverse Event (COSTART Term)	Study Phase/ Tx & Dose	Resolution of Adverse Event	Relationship to Study Drug
12/BU	Bottom got very sore	Rash	After BHT / Placebo	NI	MI
	Very irritable	Nervousness	D/R / 1:100	NI	NI
	Very irritable	Nervousness	D/R / 1:100	NI	NI
	Diaper rash	Rash	D/R / 1:10	Rec. topical ointment	Concurrent illness - not related
	Virus, vomited	Infect Virus Vomit	D/R / 1:1,000	NI	NI
13/SM	Has strept throat	Infect Bact	Wk before D/R/NA	Antibiotic	Concurrent illness - not related
	another sore throat with cold	Pharyngitis Rhinitis	Prior to D/R/NA	NI	Concurrent illness - not related
	Flu bug, nausea, vomiting, diarrhea	Flu Synd	D/R / 1:1,000	NI	NI
14/ZH	Very irritable	Nervousness	After BHT / Placebo	NI	NI

BHT = Breath Hydrogen Test Phase
D/R = Dose-Response Phase
NI = Not indicated
NA = Not applicable

TABLE 8.8.5
TRIAL S-2 (OMC-SUC-2): SAFETY POPULATION
LISTING OF PATIENTS WITH ADVERSE EVENTS

Pt Number/ Initials	Adverse Event (Original Term)	Adverse Event (COSTART Term)	Study Phase/ Tx & Dose	Resolution of Adverse Event	Relationship to Study Drug
15/PV	Upset stomach, nausea	Dyspepsia Nausea	During BHT / Placebo	NI	NI
	Moderate headache	Headache	After BHT / Placebo	NI	NI
	Weight drop 1.5 lbs,	Weight Dec	Betw. BHT #1	NI	Concurrent illness - not related
	still bruising	Ecchymosis	& BHT #2 / NA		
	Weight gain	Weight Inc	After BHT / Enzyme	NI	NI
	Felt sick, nausea, cramps, freq BM's	Nausea Pain Abdo Diarrhea	Betw. BHT #2 & BHT #3/NA	NI	Possibly related
	Headache	Headache	D/R / 1:100	NI	Possibly related
17/SF	Irritable for 2 days, diff sleeping for 24 h	Nervousness Insomnia	After BHT / Enzyme	NI	Possibly related
	Unable to sleep	Insomnia	After BHT / Milk & Enzyme	NI	Possibly related

BHT = Breath Hydrogen Test Phase
D/R = Dose-Response Phase
NI = Not indicated
NA = Not applicable

TABLE 8.8.5
TRIAL S-2 (OMC-SUC-2): SAFETY POPULATION
LISTING OF PATIENTS WITH ADVERSE EVENTS

Pt Number/ Initials	Adverse Event (Original Term)	Adverse Event (COSTART Term)	Study Phase/ Tx & Dose	Resolution of Adverse Event	Relationship to Study *Drug*
18/EF	A lot spit out	Saliva Inc	During BHT / Milk & Enzyme	NI	NI
	Ear infection	Infect	Prior to D/R / NA	Antibiotic	NI
	Diarrhea and cramping while on amoxicillin	Diarrhea Pain Abdo	Between BHT & D/R/NA	NI	Concurrent illness - not related
	Thinks that she has tonsillitis (on 4/4/94 reported as "was viral sore throat")	Pharyngitis	D/R/Full strength	NI	Concurrent illness - not related
	Has ear infections	Infect	D/R/Full strength	Antibiotic	Concurrent illness - not related
19/RG	Vomited	Vomit	During BHT / Enzyme	NI	NI
	Ear infection on day 3	Infect	After BHT / Milk & Enzyme	Antibiotic	Concurrent illness - not related
	Flu like symptoms	Flu Synd	After BHT / Milk & Enzyme,	NI	NI

BHT = Breath Hydrogen Test Phase
D/R = Dose-Response Phase
NI = Not indicated
NA = Not applicable

TABLE 8.8.5
TRIAL S-2 (OMC-SUC-2): SAFETY POPULATION
LISTING OF PATIENTS WITH ADVERSE EVENTS

Pt Number/ Initials	Adverse Event (Original Term)	Adverse Event (COSTART Term)	Study Phase/ Tx & Dose	Resolution of Adverse Event	Relationship to Study Drug
20/SW	Nausea & vomiting	Nausea Vomit	During BHT / Placebo	NI	NI
	Lots of gagging	Vomit	During BHT / Enzyme	NI	NI
	Fever 103 degrees	Fever	D/R / 1:100	Antibiotic & Tylenol	Concurrent illness - not related
	Fever 101 degrees,	Fever	D/R / 1:100	NI	Concurrent illness - not related
	Strep throat	Infect Bact			
21/KR	Severe lower abdominal pains	Pain Abdo	D/R / 1:100	Saw pediatrician	Possibly related
	Constipation possibly related to enzyme	Constip	D/R / 1:100	NI	Possible related
22/MT	Vomited	Vomit	During BHT / NI	NI	Possible related
	Ear infection	Infect	Betw. BHT #1 & BHT #2 / NA	Antibiotic	Concurrent illness - not related

BHT = Breath Hydrogen Test Phase
D/R = Dose-Response Phase
NI = Not indicated
NA = Not applicable

TABLE 8.8.5
TRIAL S-2 (OMC-SUC-2): SAFETY POPULATION
LISTING OF PATIENTS WITH ADVERSE EVENTS

Pt Number/ Initials	Adverse Event (Original Term)	Adverse Event (COSTART Term)	Study Phase/ Tx & Dose	Resolution of Adverse Event	Relationship to Study Drug
23/RT	Stoma irritated & red	Rash	Betw. BHT #1 & BHT #2 / NA	Use powder/paste PRN	Concurrent illness - not related
	Surgery	React Unevai	Betw. BHT & D/R / NA	Closure of colostomy	Concurrent illness - not reiated
	Constipation on full dose enzyme	Constip	NI / NI	NI	Possibly related
	Face looked bloated	Edema Face	D/R / 1:100	NI	Possibly related
24/CH	Runny nose, teething,	Rhinitis	Wk. before D/R / NA	Antibiotic	Concurrent illness - not related
	ear infection	React Uneval Infect		(Septra)	
	Vomited after antibiotic after dinner	Vomit	D/R / 1:1,000	NI	Concurrent illness - not related
	Projectile vomiting, skin grey, lips white, went shocky	Shock	D/R / 1:1,000	To E.R.-hold enzyme - gave Pedialyte	Possibly related
	Miserable, screaming	React Uneval	During D/R / NA	D/R phase suspended	NI
	Diaper rash	Rash	D/R Phase / full strength	Cleared up in one day	Concurrent illness - not related

BHT = Breath Hydrogen Test Phase
D/R = Dose-Response Phase
NI = Not indicated
NA = Not applicable

TABLE 8.8.5
TRIAL S-2 (OMC-SUC-2): SAFETY POPULATION
LISTING OF PATIENTS WITH ADVERSE EVENTS

Pt Number/ Initials	Adverse Event (Original Term)	Adverse Event (COSTART Term)	Study Phase/ Tx & Dose	Resolution of Adverse Event	Relationship to Study Drug
27/JW	Vomited	Vomit	During BHT / Milk & Enzyme	NI	Possibly related
	Earache	Pain Ear	Betw. BHT & D/R / NA	NI	Concurrent illness - not related
	Dehydration	Dehydrat	Betw. BHT & D/R / NA	Adm. to hosp. for rehydration	Possibly related
	Nausea, vomiting, diarrhea	Nausea Vomit Diarrhea	Betw. BHT & D/R / NA	NI	Concurrent illness - not related
	Mass on "R" breast	Neopl Breast	Betw. BHT & D/R / NA	Surgery--benign mass	Concurrent illness - not related
	Dehydration, bilat ear infections, flu-like symptoms	Dehydrat Infect Flu Synd	Betw. BHT & D/R / NA	Adm. to hosp. for rehydration	Concurrent illness - not related
	Bottom sore	Rash	D/R / 1:100	NI	Concurrent illness - not related
	Might be getting a cold	Rhinitis	D/R / 1:10	NI	Concurrent illness - not related

BHT = Breath Hydrogen Test Phase
D/R = Dose-Response Phase
NI = Not indicated
NA = Not applicable

TABLE 8.8.5
TRIAL S-2 (OMC-SUC-2): SAFETY POPULATION
LISTING OF PATIENTS WITH ADVERSE EVENTS

Pt Number/ Initials	Adverse Event (Original Term)	Adverse Event (COSTART Term)	Study Phase/ Tx & Dose	Resolution of Adverse Event	Relationship to Study Drug
28/SHW	Abdominal distention	Abdo Enlarge	After BHT / Milk & Enzyme	NI	NI
	Clear runny nose. May have a bug	Rhinitis	D/R / 1:100	NI	Concurrent illness - not related
	Cough	Cough Inc	D/R / 1:100	NI	Concurrent illness - not related
	Clear runny nose	Rhinitis	D/R / 1:100	NI	Concurrent illness - not related
	Fever	Fever	D/R / 1:100	NI	Concurrent illness - not related
	Runny nose	Rhinitis	D/R / 1:1,000	NI	NI
29/AT	Increased frequency of urine output	Urin Frequency	During BHT / Placebo	NI	Concurrent illness - not related
31/KF	Vomiting	Vomit	After BHT / Milk & Enzyme	NI	NI
	Symptoms suggestive of URI	Pharyngitis	NI / NI	Antibiotic	Concurrent illness - not related

BHT = Breath Hydrogen Test Phase
D/R = Dose-Response Phase
NI = Not indicated
NA = Not applicable

TABLE 8.8.5
TRIAL S-2 (OMC-SUC-2): SAFETY POPULATION ,
LISTING OF PATIENTS WITH ADVERSE EVENTS

Pt Number/ Initials	Adverse Event (Original Term)	Adverse Event (COSTART Term)	Study Phase/ Tx & Dose	Resolution of Adverse Event	Relationship to Study Drug
32/LD	Nausea/ bright abdominal pain - hunger	Nausea Pain Abdo	During BHT / Enzyme	NI	Possibly related
	Large volume of emesis	Vomit	During BHT / Placebo	NI	Concurrent illness - not related
33/LS	No symptoms described	React Uneval	NI / NI	Antibiotics	Concurrent illness - not related
	No symptoms described	React Uneval	NI / NI	Antibiotics	Concurrent illness - not related
34/TB	Stomach ache	Pain Abdo	During BHT / Enzyme	NI	NI
	V. small amount of emesis	Vomit	During BHT / Placebo	NI	Concurrent illness not related
	Intestinal virus	Infect Virus	D/R / Full strength (1 day) & 1:1,000	NI	Concurrent illness - not related
	Excessive diarrhea and cramping	Diarrhea Pain Abdo	D/R / 1:1,000	Mom suspicious viral in origin	Possibly related

BHT = Breath Hydrogen Test Phase
D/R = Dose-Response Phase
NI = Not indicated
NA = Not applicable

TABLE 8.8.5
TRIAL S-2 (OMC-SUC-2) : SAFETY POPULATION
LISTING OF PATIENTS WITH ADVERSE EVENTS

Pt Number/ Initials	Adverse Event (Original Term)	Adverse Event (COSTART Term)	Study Phase/ Tx & Dose	Resolution of Adverse Event	Relationship to Study Drug
36/RZ	Abdominal pain,	Pain Abdo	After BHT / Placebo	NI	Concurrent illness - not related
	sore throat,	Pharyngitis			
	general **malaise**,	Malaise			
	temperature of 100.9	Fever			
37/SK	Notation refers to replacing enzymes "prior to illness"	React Uneval	Betw. BHT & D/R / NA	NI	NI

BHT = Breath Hydrogen Test Phase
D/R = Dose-Response Phase
NI = Not indicated
NA = Not applicable

Withdrawals Due to Adverse Events

Patient 6 was the only patient who withdrew from the clinical trial due to an adverse event. The patient starting wheezing 90 minutes after receiving sacrosidase treatment and was taken to the emergency room and admitted to the intensive care unit. The patient was subsequently withdrawn from the trial for this event. The wheezing was considered a serious adverse event and is described in more detail below.

Serious Adverse Events

A serious adverse event included any event that was fatal or life-threatening, was permanently disabling, required inpatient hospitalization, or was a congenital anomaly, cancer or overdose. For the purpose of this trial, this definition was extended to events which required an emergency room visit, even if the patient was not admitted to the hospital.

There were no deaths in this trial, but there were four patients who experienced serious adverse events. All of these events were classified as serious 'because they were associated with hospitalization or at least a visit to a hospital emergency room even if the patient was not admitted. The four patients who experienced serious adverse events are presented in Table 8.8.6, and brief narrative summaries that describe these events for each patient follow.

patient 6 was a 48-month-old male who was first treated with sacrosidase on 6/16/93. There were no adverse events reported following this initial treatment. On 6/23/93, the patient starting wheezing 90 minutes after receiving 2 mL of full strength sacrosidase orally during the breath hydrogen phase of the trial. The patient was taken to the emergency room and subsequently admitted to the intensive care unit. He was discharged from the hospital the following day, and was then scheduled to be seen by an allergist. The mother reported that the child had asthma and had been treated with steroids (likely prednisone, but confirmation was not available) for this condition at 5 mg BID, but had been tapered down to 5 mg qd prior to his first dose of sacrosidase on 06/16/93. The patient's asthma and steroid treatment had not been reported to either the Clinical Investigator or trial coordinator prior to this adverse event. The sacrosidase was discontinued and the patient was withdrawn from the trial because of this event. In the opinion of the Clinical Investigator, this event was possibly related to sacrosidase. The severity of this event was not recorded. The patient was subsequently rechallenged by skin testing with the sacrosidase solution. The allergist reported that the skin test was positive.

Patient 23 was a 6-month-old female who was first treated with sacrosidase on 3/21/94. On 1/27/94, the patient's stoma was irritated and red. These symptoms were treated with powder/paste as needed. On 4/7/94, the patient underwent elective surgery for closure of colostomy. Source documents indicate that the surgery was performed between the breath hydrogen and dose-response phases of this trial. The patient recovered from surgery, completed the trial, and then continued on open-label sacrosidase with meals and snacks. In the opinion of the Investigator, these events were not related to sacrosidase. The severity of each event was not recorded.

Patient 24 was an 8-month-old female who was first treated with sacrosidase on 9/7/94. On 9/20/94, the patient was started on Septra® (sulfamethoxazole and trimethoprim) for otitis media of the left ear; this was the same day the patient started treatment with the 1:1,000 dilution of sacrosidase in the dose-response phase of the trial. The patient vomited immediately after her Septra® dose following dinner; the outcome of this event was not available. On 9/22/94, the patient experienced projectile vomiting, and had gray skin and white lips. She was admitted to the emergency room for these symptoms the same day, and subsequently vomited mucous; her color came back. In addition, "congestion" and "red ear" were also reported. Treatment with sacrosidase was interrupted for theses events on 9/22/94, but restarted on 10/11/94. The patient completed the trial, and continued on open-label sacrosidase with meals and snacks. In the opinion of the Investigator, the vomiting that followed Septra® treatment was not related to sacrosidase. The Investigator considered the projectile vomiting, gray skin, and white lips to be possibly related to sacrosidase. The severity of each event was not recorded.

Patient 27 was a 47-month-old male who was first treated with sacrosidase on 11/15/94. On 12/19/95, the patient was dehydrated and admitted to the hospital for re-hydration. The hospital discharge date and the outcome of this event were both not available. On 12/20/95 the patient experienced nausea, vomiting, and diarrhea. The outcomes of theses events were not available. The sacrosidase was stopped on 01/17/95 for an unspecified reason following treatment with milk/sacrosidase. On 02/02/96, the patient underwent same-day surgery for removal of a benign mass in his right breast. Following discharge, the patient because dehydrated and was re-admitted to the hospital for rehydration. It was thought that this episode of dehydration was related to the anesthesia that had been administered for the operation. The outcome of this event was "apparently satisfactory." Source documents indicate that sacrosidase treatment was re-started on 03/16/96 to begin the dose-response phase of the trial. The

patient completed the trial and was continued on open-label sacrosidase with meals and snacks. In the opinion of the Clinical Investigator, the first episode of dehydration was considered to be possibly related to sacrosidase. The Investigator considered the nausea, vomiting, diarrhea, mass on right breast, and second episode of dehydration (following surgery) to be unrelated to sacrosidase. The severity of each event was not recorded.

Patients Withdrawn from Controlled Trials

A list of patients who withdrew from each of the two controlled trials after treatment was initiated is given in Tables 8.8.7 and 8.8.8 for Trials S-l and S-2, respectively. It shows that four patients withdrew from the first trial (S-l) and six from the second trial (S-2). Of these, only one withdrew due to an adverse event. This was patient 6 in Trial S-2.

Table 8.8.7

TRIAL NO. S-l (OMC-SUC-1): Safety Population
Listing of Patients Who Withdrew from Study After Treatment"

Patient Number	Treatment Sequence (Breath Hydrogen)[b]	Treatment Sequence (Dose-Response)[c]	Study Phase/Period at Time of Withdrawal	Reason for Withdrawal
3	PE	NI	Dose-Response/2	Lost to Follow-up (Only 2 S&S Diaries Returned)
4	NI	NI	Dose-Response/3	Lost to Follow-up (Only 2 S&S Diaries Returned)
11	PE	NI	Between Breath Hydrogen and Dose-Response	Lost to Follow-up (No S&S Diaries Returned)
12	PE	NI	Between Breath Hydrogen and Dose-Response	Lost to Follow-up (No S&S Diaries Returned)

'Received placebo or enzyme.
[b]p = Placebo, E = Enzyme; S&S = Stooling and Symptom
NI = Not Indicated
Note: Patient 4 is not in the safety population, but did withdraw from the study.

TABLE 8.8.8

TRIAL NO. S-2 (OMC-SUC-2): SAFETY POPULATION
LISTING OF PATIENTS WHO WITHDREW FROM STUDY
AFTER TREATMENT[a]

Patient Number	Treatment Sequence (Breath Hydrogen/^[b]	Treatment Sequence (Dose-Response)[c]	study Phase/Period at Time of Withdrawal	Reason for Withdrawal
2	EPM	ADCB	Breath Hydrogen/2	Child had difficulties completing third breath hydrogen test. Difficulties were such that a repeat test was required to obtain accurate test results. Family refused to repeat third breath hydrogen test.
5	UK	BCAD	Breath Hydrogen/l	Discontinued due to symptoms experienced by brother (Patient 6).
6	EPM	CADB	Breath Hydrogen/2	Began wheezing during second breath hydrogen test; study discontinued.
22	UK	CADB	Breath Hydrogen/l	After the informed consent was signed, patient had two placebo BHT's done. Because both tests were negative, the patient was dropped from the study.
29	EPM	DBCA	Breath Hydrogen/3	Mother requested to withdraw due to difficulties encountered getting child to take enzyme solution during the dose-response phase.

"Received at least one of the following treatments: placebo, enzyme, milk/enzyme.
[b]P = Placebo, E = Enzyme, M = Milk/Enzyme, UK = Unknown.
[c]A = Full-strength enzyme, B = 1:10 dilution, C = 1:100 dilution, D = 1:1,000 dilution.

TABLE 8.8.8

TRIAL NO. S-2 (OMC-SUC-2): SAFETY POPULATION
LISTING OF PATIENTS WHO WITHDREW FROM STUDY
AFTER TREATMENT[a]

Patient Number	Treatment Sequence (Breath Hydrogen)[b]	Treatment Sequence (Dose-Response)[c]	study Phase/Period at Time of Withdrawal	Reason for Withdrawal
36	UK	BACD	Breath Hydrogen/l	Disaccharidase levels provided by the referring physician did not clearly indicate that this patient met study criteria. Because diagnostic BHT's had not been done, it was decided to enroll the patient in the protocol and collect data routinely collected during the week prior to BHT's and schedule the placebo test first. The results of the placebo test were normal, therefore it was determined that the patient did not meet the study criteria. Testing was discontinued.

[a]Received at least one of the following treatments: placebo, enzyme, milk/enzyme.
[b]P = Placebo, E = Enzyme, M = Milk/Enzyme, UK = Unknown.
[c]A = Full-strength enzyme, B = 1:10 dilution, C = 1:100 dilution, D = 1:1,000 dilution.

Relevant Experimental Data under 16 CFR 1702.9 (b)

Nonclinical Toxicology Summary for Sacrosidase

Orphan Medical proposes to use sacrosidase for the treatment of congenital sucrase-isomaltase deficiency (CSID) patients. The purpose of this discussion is to provide a summary of the available nonclinical toxicology information on sacrosidase.

An initial review of the literature was undertaken; using the computerized databases of the National Library of Medicine via the TOXNET and TOXLINE databases. The search used "sacrosidase" as a text word; subsequent searches were refined based upon the initial information derived, and may have keyed to authors name, specific data types (e.g. mutagenicity, metabolism), etc.

At the request of FDA during a pre-NDA meeting in October 1996 another and more comprehensive literature search was conducted. That search also failed to identify any literature relating to the toxicology of this protein.

A waiver of nonclinical pharmacology tests was requested to the FDA based on the following:

1. The enzyme is an exogenous replacement or substitution of a missing endogenous one.
2. There are no appropriate animal models.
3. Efficacy has been clearly demonstrated in humans.

Adsorption, Distribution, Metabolism and Excretion

Based on the extensive data base associated with use of this drug in humans, the long-term use of sacrosidase in the baking and confectionery industry and the lack of toxicity associated with this material ADME and LD50 studies have not been conducted.

Metabolism of Drug

Because sacrosidase is a large macromolecule, it will not be transported across the gastrointestinal mucosa and into the systemic circulation following oral ingestion. Thus, no systemic toxicity testing directly from the sacrosidase molecule is feasible. Sacrosidase is a naturally occurring enzyme with a glycoprotein structure, it will be digested to peptides and eventually amino acids within the small intestine. These metabolic products will be absorbed into the circulation and utilized as nutrients.

Several years of clinical experience with the yeast-derived oral sacrosidase solution in patients as young as 5 months of age have not revealed any evidence of significant toxicity or intolerance.

HUMAN EXPERIMENTAL DATA INVOLVING THE TESTING OF HUMAN SUBJECTS

Orphan Medical Inc., assures the Commission that for all human experimental data submitted with this petition that adequate measures have been taken to ensure against psychological or physical injury to the subjects of the human studies. These studies were conducted in compliance with 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 56 (Institutional Review Boards), and meet the criteria under 16 CFR part 1028.

PRODUCT SPECIFICATIONS

Complete quantitative formula for the product

The final dosage form is sacrosidase (8,500 IU/mL) solution composed of a 50%:50% glycerin:water mixture.

Listing of all dosage forms in which the product is available

The final and only dosage form consists of a 118 mL blow-molded, low density polyethylene resin bottle which contains a solution of:

Component:	per mL	per bottle (118 mL):
Sacrosidase solution in 50% glycerin/SO% water	8,500 I.U.	1,003,000 I.U.

The dosage of sacrosidase is titrated based on the patient's weight and symptoms.

Amount Taken	Weight
1 mL	<15 kg with each meal or snack
2 mL	>15 kg with each meal or snack

Each 1 mL is equivalent to 22 drops of the solution metered through the pierced tip.

PACKAGING SPECIFICATIONS

Name of manufacturer of the package
The facility involved in the manufacture of Sucraid™ (sacrosidase) oral solution is:

NutraMax Products, Inc.
9 Blackburn Drive
Gloucester, MA 01930

Specifications for the package

Container/closure

The drug product is packaged in a hermetically sealed, 118 mL bottle, formed using blow, fill, seal technology, at the time the product is filled. The bottle has a threaded top and a dropper tip which is compatible with the piercing cap.

Specification: See attached specification

The [redacted]ap is made [redacted] and is manufactured by Unicon Container Corporation. The cap is placed on the sealed bottle after filling. The cap has a small spike on the inside which can be used to pierce the sealed bottle tip at the time of first use.

Specification: See attached specification

Scoop

The scoop is made [redacted] which is composed of [redacted] and is manufactured by Measurex, S & L Plastics, Inc. It is suitable for food contact use (21 CFR 177.1640). The scoop has no product contact except for measuring the dose.

Specification: See attached specification

Label

The label is manufactured by Labelprint Corporation. The label is constructed of 3.5 mil W-treated, flexible, opaque white olefin film.

Specification: See attached specification

Complete packaging description of carton

The carton is manufactured by Lowell Paper Box, Inc., from 16 point Solid Bleach Sulfate Paperboard line with 0.5 mil polyethylene. Its dimensions (upon closing) are 3½ X 1¼ X 6 1/8. The paperboard folding carton for Sucraid (sacrosidase) oral solution holds two bottles and one scoop. The cartons upon receipt must meet manufactures specification for contaminates, color, and defects using Mil Standard 105e General Inspection Level I. Defects are defined as critical (<0.25%), major (0.25%), minor (2.5%).

Description of each size product offered

Size:	118 mL
Physical Form:	LDPE translucent bottle
Color:	slight yellow
Flavoring:	none added; sweet

LABELING AND PACKAGING SAMPLES

Provided are three Sucraid dual pack cartons, containing investigational labeling, and scoop.

DRAFT PACKAGE INSERT

Sucraid™ (sacrosidase) oral solution

DESCRIPTION

Sucraid™ (sacrosidase) oral solution is an enzyme replacement therapy for use in the treatment of congenital sucrase-isomaltase deficiency (CSID). Each milliliter (mL) of Sucraid contains 8,500 International Units (I.U.) of the enzyme sacrosidase chemical name β,D-fructofuranoside fructohydrolase, which is derived from baker's yeast (*Saccharomyces* cerevisiae). Sucraid also contains glycerin (glycerol) in an aqueous solution.

Sucraid is a pale yellow, clear solution with a pleasant sweet taste. Sacrosidase has an apparent molecular weight of 97 kD. It is fully soluble with water, milk, fruit juice, and infant formula (DO NOT HEAT).

CLINICAL PHARMACOLOGY

Congenital sucrase-isomaltase deficiency (CSID) is a chronic malabsorption disease characterized by an autosomal recessive inheritable disease of sucrase and isomaltase deficiency. CSID is characterized by a complete or almost complete lack of endogenous sucrase activity, a marked reduction in isomaltase activity, and a moderate decrease in maltase activity.

Sucrase is a naturally-occurring enzyme that is produced in the brush border of the small intestine, primarily in the distal duodenum and jejunum. Sucrase hydrolyzes sucrose, a disaccharide, into its component monosaccharides, glucose and fructose.

In the absence of the endogenous human enzyme, sucrose is not metabolized and is not absorbed by the intestines. The presence of the intact disaccharides in the intestinal lumen leads to the osmotic retention of water, resulting in loose stools. Unabsorbed sucrose in the large intestine is fermented by bacterial flora to produce hydrogen, methane, and water. These gases generate gastrointestinal discomfort including excessive gas, bloating, abdominal cramps, watery diarrhea, nausea, and vomiting. As a result, undiagnosed CSID patients often fall behind in their expected growth and development curves and fail to thrive. Chronic malabsorption results in malnutrition.

Measurement of expired breath hydrogen under controlled conditions following a sucrose challenge (a measurement-of excess hydrogen excreted in exhalation) in CSID patients have shown levels as great as 6 times that of normal subjects. Expert opinion defines clinical CSID as a condition having the following features: stool pH of less than 6, an increase in breath

hydrogen of greater than 10 ppm when challenged with sucrose after fasting, and a negative lactose breath test.

Sucraid administered with meals to patients with CSID has been shown in controlled clinical trials to decrease stool frequency and watery diarrhea, improve stool consistency, and decrease abdominal pain, bloating, and gas. In a retrospective study, a number of patients showed improved growth as evidenced by weight for height and weight for age measurements. In addition, sleep disturbances secondary to gastrointestinal symptoms have been alleviated in some patients taking Sucraid. Associated breath hydrogen excretion levels were more indicative of normalized digestion of sucrose.

CSID is often a difficult disease to diagnose. Studies have shown that in pediatric patients with chronic diarrhea of unknown origin that 4-10% had CSID. Because of the difficulties of diagnosing CSID, it may be warranted to conduct a short therapeutic trial (e.g. one week) to assess patient response in those suspected of having CSID.

CLINICAL STUDIES

Clinical trials were conducted to assess the safety and effectiveness of sacrosidase. The first controlled trial was published by WR Treem, et al. The second of the controlled trials is in preparation for publication by WR Treem, et al. These publications discuss additional aspects of treating CSID patients that may be useful for treating physicians.

INDICATIONS AND USAGE

Sucraid is an oral enzyme replacement therapy indicated for the treatment of confirmed or suspected congenital sucrase-isomaltase deficiency (CSID) and the prevention of the associated symptoms of sucrose malabsorption such as frequent watery stools, gas, bloating, abdominal cramping, explosive diarrhea, and growth retardation.

CONTRAINDICATIONS

Patients known to be hypersensitive to yeast, yeast products, or glycerin (glycerol).

PRECAUTIONS

General: Diabetics should be aware that the use of Sucraid will enable sucrose (and products of its hydrolysis - glucose and fructose) to be absorbed and this must be carefully considered in dietary planning. Although Sucraid provides replacement therapy for the deficient sucrase enzyme, it does not provide specific replacement therapy for isomaltase deficiency. Therefore, it may be necessary to continue a restriction in the starch content of the diet in order for patients to optimize diminishment of disease symptoms. The necessity for dietary starch restriction

for patients using Sucraid should be evaluated on a case by case basis.

Information for patients: See Patient Package Insert. Patients should be instructed 'to discard bottles of Sucraid 4 weeks after first opening due to the potential for bacterial growth.

Laboratory tests: A positive breath hydrogen test following oral challenge with sucrose and a negative breath hydrogen test following oral challenge with lactose along with a stool pH of less than 6 provides an acceptable diagnosis of CSID. Due to the high incidence of false-negatives in the breath hydrogen test, a therapeutic challenge with Sucraid may be warranted.

The definitive test for diagnosis of CSID has remained the measurement of intestinal disaccharidases following small bowel biopsy.

Prior to the advent of the breath hydrogen test, oral sucrose tolerance tests were utilized for the noninvasive diagnosis of CSID. In children, a rise of blood glucose of >20 mg/dl after a 2.0 g/kg sucrose load is considered an indication of sucrose malabsorption. However, there is a high incidence of false-positive tests using sucrose challenge followed by glucose blood levels due to delayed gastric emptying.

Differential urinary disaccharide testing has been utilized by some physicians for diagnosis of disaccharidase deficiencies. Administration of lactulose, lactose, sucrose, isomaltose, and rhamnose following an overnight fast, with collection of urine for 10 hours and separation of the sugars by thin layer chromatography, has demonstrated excellent agreement with small intestinal biopsy for diagnosis of CSID.

In some situations it may be clinically inappropriate, difficult, or inconvenient to perform a small bowel biopsy or breath hydrogen test to make a definitive diagnosis of CSID. In such cases, it is possible that replacement of the suspected deficient sucrase enzyme with Sucraid for three to five days will indicate whether the patient has a deficiency of sucrase. Patients responding to Sucraid with an improvement in clinical symptoms should still be subjected to a diagnostic work-up at a later date so that the diagnosis of primary or secondary sucrase-isomaltase deficiency can be made. The effects of Sucraid have not been evaluated in patients diagnosed with secondary (acquired) disaccharidase deficiencies.

Drug interactions: There are no known drug-drug or drug-food interactions that have been reported with the use of Sucraid.

Carcinogenesis, mutagenesis, impairment of fertility: No carcinogenicity, mutagenicity, or fertility studies have been conducted with Sucraid.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with Sucraid. It is also not known whether Sucraid can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Sucraid should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The Sucraid enzyme is broken down in the stomach and intestines and the component amino acids and peptides are then absorbed as nutrients. Use of this product in pregnant or nursing mothers should be evaluated by the treating physician on a case by case basis._

Pediatric use: Sucraid has been used in patients as young as 5 months of age. Evidence from two controlled trials and one uncontrolled trial in primarily pediatric patients show that Sucraid is safe and effective for the treatment of CSID.

ADVERSE REACTIONS

Adverse experiences with Sucraid in clinical trials were generally minor and **were** frequently associated with the underlying disease. In clinical studies of up to 54 months duration, physicians treated a total of 52 patients with Sucraid. The adverse experiences and respective number of patients reporting each event (in parenthesis) were as follows: abdominal **pain** (4), vomiting (3), nausea (2), diarrhea (2), constipation (2), insomnia (1), headache (1), nervousness (1), facial edema (1), and dehydration (1). One asthmatic patient experienced an acute hypersensitivity reaction (wheezing) to Sucraid which resolved with no sequelae. Care should be taken to administer Sucraid for the first time at a facility where acute hypersensitivity reactions can be adequately treated. Alternatively, the patient may be tested for hypersensitivity to Sucraid through skin abrasion testing. Should symptoms of hypersensitivity appear, discontinue medication and initiate symptomatic and supportive therapy if indicated.

OVERDOSAGE

No incidents of overdosage have been reported. Glycerin, a component of Sucraid, is an osmotic diuretic. If an overdose should occur, adequate hydration should be maintained.

DOSAGE AND ADMINISTRATION

The recommended dosage is 1 to 2 mL, or 1 to 2 full measuring scoops (each full measuring scoop equals 1 mL; 22 drops from the bottle tip equals 1 mL) taken orally with each meal or snack diluted with 2 to 4 ounces of water, milk, fruit juice, or infant formula. The beverage or infant formula should be served cold or

at room temperature. The beverage or infant formula should not be warmed or heated before or after addition of Sucraid because heating is likely to decrease potency. Clinical studies have suggested that a greater portion of the enzyme is delivered to the small intestine if Sucraid is diluted with milk instead of water. This beneficial effect is believed to be due to decreased activity of intragastric pepsin in the presence of milk proteins.

It is recommended that approximately half of the dosage be taken at the beginning of each meal or snack, and the remainder be taken at the end of each meal or snack.

The recommended dosage is as follows:

- 1 mL (one full measuring scoop or 22 drops) per meal or snack for patients up to 15 kg in body weight.
- 2 mL (two full measuring scoops or 44 drops) per meal or snack for patients over 1.5 kg in body weight.

Dosage may be administered via the provided 1 mL measuring scoop or by drop count method (1 mL equals 22 drops from the bottle tip).

HOW SUPPLIED

Sucraid is available in 118 mL (4 fluid ounce) translucent plastic bottles, packaged two bottles per box. Each mL of solution contains 8,500 International Units (I.U.) of sucrase (sacrosidase). Each bottle is supplied with a plastic puncturing cap that is used to open the sealed bottle at first use, and to reseal it after each use. In addition, a 1 mL measuring scoop is provided with each bottle. A full measuring scoop is 1 mL and the gradation mark indicates one-half (1/2) mL.

NDC 62161-011-04

Store in a refrigerator at 2° - 8°C (36° - 46°F). Discard four weeks after first opening due to the potential for bacterial growth. Protect from heat and light.

Caution: Federal law prohibits dispensing without prescription.

Manufactured by:
NutraMax Products, Inc.
Gloucester, MA 01930

Distributed by:
Orphan Medical, Inc.
Minneapolis, MN 55305

For questions of a medical nature, please call Orphan Medical, Inc. toll free at 1-888-8ORPHAN (l-888-867-7426).

DRAFT PATIENT PACKAGE INSERT

Sucraid™
(sacrosidase) **oral** solution

Please read this leaflet carefully before you take Sucraid™ (sacrosidase) oral solution or administer Sucraid to **a** child. Please do not throw away this leaflet until you have finished your medicine. You may need to read this leaflet again at a later date. This leaflet does not contain all the information on Sucraid. For further information or advice, ask your doctor or pharmacist.

INFORMATION ABOUT YOUR MEDICINE

The name of your medicine is Sucraid™ (sacrosidase) oral solution. It can be obtained only with a prescription from your doctor.

The purpose of your medicine:
Sucraid is an enzyme replacement therapy for use in the treatment of congenital sucrase-isomaltase deficiency (CSID) . CSID is a condition where your 'body lacks the enzymes needed to properly break down and absorb sucrose (table sugar) and isomaltase (a type of starch) from the intestines.

The symptoms of CSID often include frequent watery diarrhea, abdominal pain, bloating, and gas. In many cases, the symptoms of CSID are similar to other medical problems. Only your doctor can make a definite diagnosis of CSID.

Sucraid can help improve the breakdown and absorption of sucrose (table sugar) from the intestine and can help relieve the symptoms of CSID. Sucraid may also possibly improve growth in young children and make it easier to sleep by relieving gastrointestinal symptoms.

Sucraid does not contain the enzyme needed to break down and absorb isomaltase (a type of starch) from the intestine. Therefore, you may need to restrict the amount of starch in your diet. Your doctor will tell you if you should restrict the amount of starch in your diet.

Discuss the following important information with your doctor before you begin to take Sucraid:
Tell your doctor **if you are allergic to, have ever-had a reaction** to, or have ever had difficulty taking yeast, yeast products, or glycerin (glycerol).

Tell your doctor if you have diabetes. You need to be aware that sucrose **(table sugar)** can **be absorbed from your diet and your**

blood glucose levels may change. Your doctor will tell you if your diet or diabetes medicines need to be changed.

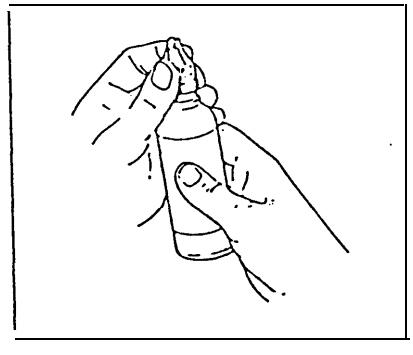
Tell *your* doctor if you are nursing a baby, are pregnant, or planning to become pregnant.

Side effects to watch for:
Some patients may experience a worsening of abdominal pain, vomiting, nausea, and diarrhea. Constipation, difficulty sleeping, headache, nervousness, and dehydration have also occurred. Other side effects may also occur. If you notice these or any other side effects during treatment with Sucraid, check with your doctor.

Stop taking Sucraid and get emergency help immediately if any of the following side effects occur: swelling, swelling of the face, or difficulty breathing.

How to take your medicine:
Each bottle of Sucraid is supplied with a plastic puncturing cap that is used to open the sealed bottle at first use and to reseal it after each use. At first use, tighten the cap until the spike in the cap punctures the bottle tip (see Figure 1). Do not use scissors or a knife to open the sealed bottle. Reseal the bottle after each use by replacing and twisting the cap until tight.

Figure 1. Puncture bottle seal with cap.



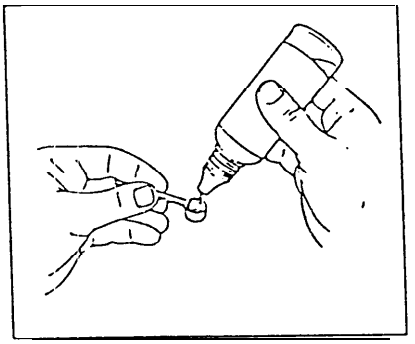
Write down the date the sealed bottle is first opened in the space provided on the bottle label. Always discard the bottle four weeks after first opening it since Sucraid contains no preservatives.

In order to get the full benefits of this medicine, it is very important to take Sucraid as your doctor has prescribed. The

usual dosage is 1 to 2 milliliters (mL) (which equals 1 to 2 full measuring scoops) with each meal or snack.

Measure your dose with the measuring scoop provided (see Figure 2). Do not use a kitchen teaspoon or other measuring device since it will not measure an accurate dose. A full measuring scoop equals 1 mL and the gradation mark on the inside of the measuring scoop indicates one-half (½) mL. A 1 mL dose is equal to one full measuring scoop or 22 drops from the bottle tip.

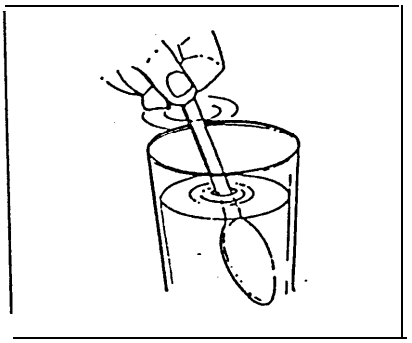
Figure 2. Measure dose with measuring scoop.



Mix your dose in 2 to 4 ounces of water, milk, fruit juice, or infant formula (see Figure 3). Clinical studies have suggested that more of the active ingredient in Sucraid is delivered to the intestine if the dose is mixed in milk instead of water.

NEVER HEAT SUCRAID O'R PUT IT IN WARM OR HOT BEVERAGES OR INFANT FORMULA. Heating Sucraid causes it to lose its effectiveness. The beverage or infant formula should be served cold or at room temperature.

Figure 3. Mix dose in beverage or infant formula.



It is recommended that approximately half of your dosage be taken at the beginning of each meal or snack, and the remainder of your dosage be taken at the end of the meal or snack.

Storing your medicine:
Sucraid is available in 4 fluid ounce **(118** mL) translucent plastic bottles, packaged two bottles per box. Each bottle is supplied with a plastic puncturing cap that is used to open the sealed bottle at first use and to reseal it after each use. In addition, a 1 mL measuring scoop is provided with each bottle.

Always store Sucraid in a refrigerator at 36° - 46°F (2° - 8°C). Protect Sucraid from heat and light.

If your bottle of Sucraid has expired (the expiration-date is printed on the bottle label), throw it away.

Keep this medicine in a safe place in your refrigerator where children cannot reach it.

Orphan Medical, Inc.
Minnetonka, Minnesota 55305

Revision Date: April, 1997

MARKETING HISTORY

Sucraid has not been marketed outside the United States.

2) JUSTIFICATION BASED UPON PACKAGING NOT BEING PRACTICAL FOR THE SUBSTANCE

Sucraid (sacrosidase) oral solution has been developed as an orphan product for the treatment of congenital sucrase isomaltase deficiency (CSID). This disease a condition which afflicts up to 0.02% of the population of North America, is an autosomal recessive disease of the small intestine characterized by an almost complete lack of endogenous sucrase activity. In the absence of sucrase activity, ingested sucrose is not broken down or absorbed in the gastrointestinal (GI) tract, leading-to symptoms of watery diarrhea, abdominal cramps, gas, and bloating. In addition, sucrose malabsorption often leads to decreased weight to height ratios, decreased weight for age, and overall failure to thrive in children with CSID.

Orphan Medical, Inc. respectfully requests an exemption from the Poison Prevention Packaging Act Requirements for Sucraid (sacrosidase) oral solution for the following reasons:

- there are no alternative drug treatments available for CSID
- the small number of afflicted patients does not make it practical to develop a child-resistant package, (estimated to be 3,000 - 10,000 cases in the United States)
- the high value associated with quality of life for the population group using the product
- the largest available child-resistant package will not contain the required dosage of Sucraid

EXEMPTION FOR A NEW DRUG

As defined in section 201(g)(1) of the Federal Food and Drug Cosmetic Act (21 U.S.C. 321 (g) (1), there have been no adverse reaction reports filed at this time under 21 CFR314.80.

A New Drug Application, NDA # 20-772, for Sucraid (sacrosidase) oral solution was submitted on May 6, 1997 and priority review granted on June 3, 1997.

Orphan Medical, Inc. understands that under 16 CFR 1702.16 that the Commission is required to deny all petitions if the FDA has not approved an NDA.

As requested by 16 CFR 11702.2, five (5) copies of this petition are enclosed herewith in addition to the original. Three (3) Sucraid investigational drug packages have been provided as requested.

All correspondence regarding this petition for exemption to the Poison Prevention Packaging Act should be directed to:

Dayton T. Reardan, Ph.D., RAC
Vice President of Regulatory Affairs
Orphan Medical, Inc.
13911 Ridgedale Drive, Suite 475
Minnetonka, MN 55305

Sincerely,

Dayton T. Reardan, Ph.D., RAC
Vice President of Regulatory Affairs
Direct: (612) 513-6969

cc: Melodi McNeil (NDA 20-772)

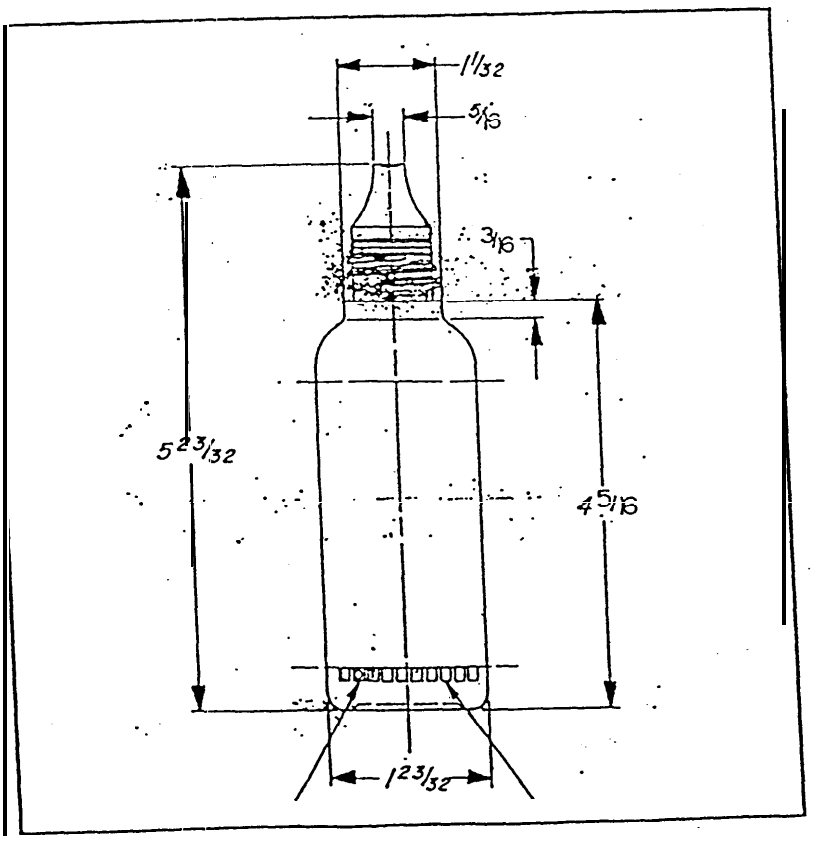
Prepared/by/Date:	[illegible] 12/12/96
Reviewed/by/Date:	[illegible] 12/12/96
Approved/by/Date:	[illegible] 12/12/96

NutraMax Products, Inc.

Pa&aging Component Specification

Packaging Component: Sucraid™ Oral Solution Bottle Revision No. 0

Technical Components	Specifications
♦ Approved Manufacturer	NutraMax Products Inc.
♦ Description	A hemetically sealed, 118 mL bottle, formed using blow, fill, seal technology, at the time the product is filled. Bottle has a threaded top and a dropper tip compatible with a 24 mm Piercing Cap
♦ Resin	Rexene PE6012.
♦ Dimensions	See Diagram below



Prepared by/Date:	Joann LaValle 4/17/97
Reviewed by/Date:	[signature] 4/17/97
Approved by/Date:	[signature] 4/17/97

NutraMax Products, Inc.

Component Inspection Release Report

Item Code Number:	G/PWRTCAP	Vendor:	Andler South Corp.
		Manufacturer:	Unicon Corp.
Component:	Sucraid™ Oral Solution 24 mm Piercing Cap	Lot No.:	
Sampled By/Date			

TEST	RESULT	SPECIFICATION	REFERENCE
Description		Closure consisting of a tapered top, ribbed exterior/threaded interior base designed to fit a 118mL spike port bottle, and a small spike on the top, interior portion of the cap.	13.613
Color		Clear	13.613
Resin[1]		Huntsman HCC 207	13.613
Spike Length		0.188" ± 0.01"	13.613
Functionality		Fits 1.18 mL spike port bottle	13.613
Defect AQL Major 0.25% Minor 4.0%		Passes	13.613

☐ Release

☐ Rejected

Quality Assurance/Date _____

'Refer to Certificate of Compliance

FINISHED PRODUCT QUALITY INSPECTION - Mil-Std-105e

PRODUCT	Sucraid™ 24mm Piercing Caps		
LOT #		LOT SIZE	

INSPECTION TYPE: ☐INITIAL RELEASE ☐REINSPECTION ☐OTHER _____

LEVEL II TABLE II A SAMPLE SIZE CODE SAMPLE SIZE BOTTLES

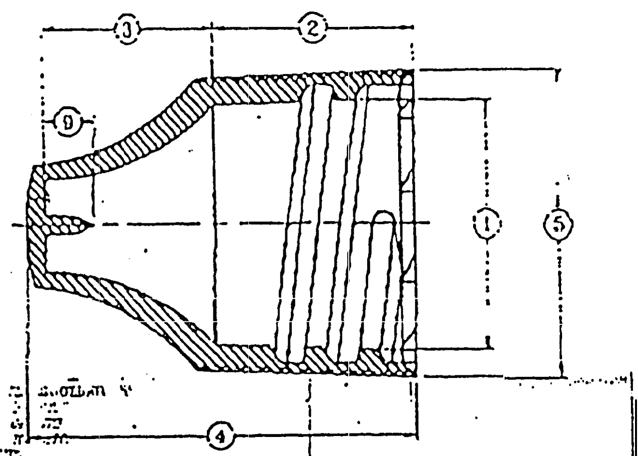
	# OF DEFECTS
I. CRITICAL	
AQL 0% accept 0 reject 1	
A. Incorrect Cap	
B. Incorrect Cap Color	
C. Incorrect Size Cap	
D. Deformed Missing Threads	
II. MAJOR "A"	
AQL 0.25% accept __ reject _	
A. Missing Spike	
B. Excess Plastic at Opening of Cap	
I. MINOR "B"	
AQL 4.0% accept __ reject _	
A. Embedded Off Color Particles	
B. Missing Opening Groves on Cap (removal)	
C. Loose safety seals	
TOTAL DEFECT	

☐Passes
☐Fails

Performed by/date_____

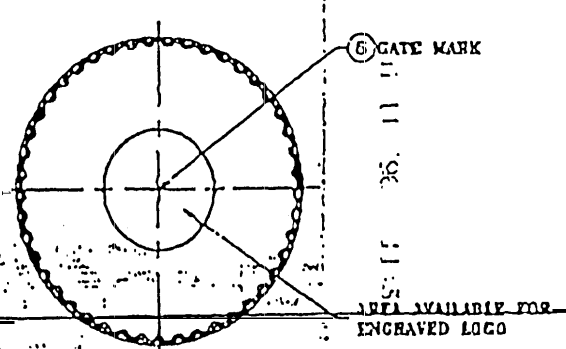
Reviewed by/date_____

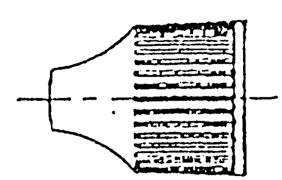
CARAC.	MEDIO	MAX.	MIN.	FRECUENCIA
1	.844	.854	.834	Vernier 1 vez/turno
2	.718	.728	.708	Vernier Comienzo
3	.818	.828	.808	Depth Mike 1 vez/turno
4	1.402	1.412	1.392	Vernier Comienzo
5	1.031	1.041	1.021	Vernier Comienzo
6	Gate alto			Visual 1 vez/turno
8	Contaminación, "Gaub", deformación, volcado y zonas defectuosas			Visual 1 vez/turno
9	.188	.198	.178	Dial Indicator Comienzo



LEGEND:
1- MINOR THREAD DIAMETER 'E'
2- BOTTOM TO SHOULDER 'F'
3- TIP TO SHOULDER
4- OVERALL LENGTH
5- OUTSIDE DIAMETER
6- GATE MARK
8- OTHER
9- PIERCE MEASURE

NOTA: DIMENSIONES EN PULGADAS A MENOS QUE SE ESPECIFIQUE LO CONTRARIO.





D	CHARAC. 6 ADDED. CHARAC. 9 WAS CHARAC. 7. GATE WAS REPLACED BY HOOK GATE. INST. (CHARAC. 3) WAS VERNIER, NOW DEPTH MIKE.	I.D.L. 08-08-86
REV. LTR.	— REVISIONS —	APPR. DATE

TITLE: 24mm. PIERCING CAP

CUSTOMER: STOCK

MATERIAL: POLYSTYRENE

unicon — Guaynabo, Puerto Rico 00970

DRAWN BY: I.D.L. | DATE: 08-28-86 | SCALE: NONE | PART NO. 1520-A

FACTORY DRAWING

Prepared by/Date:	78 3/20/97
Reviewed by/Date:	3/20/97
Approved by/Date:	3/20/97

NutraMax Products, Inc.

Component Inspection Release Report

Item Code Number:	G/PWRTSPOON1ML	Vendor:	S&L Plastics, Inc.
		Manufacturer:	S&L Plastics, Inc.
Component:	Sucraid™ Oral Solution 1 ml Dosing Spoon	Lot No:	
Sampled By/Date:			

TEST	RESULT	SPECIFICATION	REFERENCE
Description		1 ml spoon used for measuring out specified amounts of product. It consists of a long narrow handle and slightly tapered reservoir at one end. There is a line (molded into the bowl) indicating 0.5 ml.	13.615
Color		White, meets standard	13.615
Length		7.6 cm	13.615
Bowl Diameter		1.7 cm (as measured from the open end)	13.615
Bowl Depth		0.7 cm	13.615
Resin'		API 375 &API 550	13.615
Defect AQL Major 0.25% Minor 4.0%		Passes	13.615

☐ Release

☐ Rejected

Quality Assurance/Date _____

'Refer to Certificate of Compliance

FINISHED PRODUCT QUALITY INSPECTION - Mil-Std-105e

PRODUCT	Sucraid™ 1mL Dosing Spoon	
LOT #		LOT SIZE

INSPECTION TYPE: ❑ INITIAL RELEASE ❑ REI-NSPECTION ❑ OTHER_____

SEVERITY LEVEL	TABLE IIA	SAMPLE SIZE CODE	SAMPLE SIZE	BOTTLES

	# OF DEFECTS
I. CRITICAL	
AQL 0% accept 0 reject 1	
A. Incorrect Spoon	
B. Incorrect Color Spoon	
C. Incorrect Size Spoon	
D. Incorrect Resin Type	
E. Missing Handle	
II. MAJOR "A"	
AQL 0.25% accept__ reject_	
A. Sharp Edges of Spoon	
I. MINOR "B"	
AQL 4.0% accept__ reject_	
A. Embedded Off Color Particles	
B. Short Handle	

☐Passes
☐Fails

TOTAL DEFECT

Performed by/date_____

Reviewed by/date_____

NutraMax Products, Inc.

FINISHED PRODUCT QUALITY INSPECTION - Mil-Std-105e

PRODUCT:	Sucraid™ Labels (Bottle & Shipping Carton)		
LOT #:		LOT SIZE:	

INSPECTION TYPE: ☐INITIAL RELEASE ☐REINSPECTION ☐OTHER_____

LEVEL: S-1	TABLE: IIA	SAMPLE SIZE CODE:	SAMPLE SIZE:	BOTTLES

		# OF DEFECTS
I. CRITICAL		
AQL 0%	accept 0 reject 1	
A. Incorrect Label		
B. Incorrect Text		
C. Missing Text		
D. Incorrect UPC Code		
E. UPC Unscannable		
F. Foreign Matter on Label		
II. MAJOR "A"		
AQL 0.25%	accept ___ reject ___	
A. Text Printed Off-Center		
B. Poor Print Quality		
C. Foreign Matter on Label		
III. MINOR "B"		
AQL 4.0%	accept ___ reject ___	
A. Wrinkled Label		
B. Ink spots on Label		
C Slight Label Size Variation		
	TOTAL DEFECT	

❑ Passes

☐Fails

Performed by/date_ _____

Reviewed by/date_ _____

Form QA-34-23 Rev 0 4/97

SOP# 26.103